PATTON BOGGS LLP
ATTORNEYS AT LAW

2550 M Street NW
Washington, DC 20037-1350
202-457-6000
Facsimile 202-457-6315

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VIA HAND-DELIVERY

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Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Docket No. 98N-0148
64 Federal Register 1629 (Jan. 11, 1999)

Comments of the Dietary Supplement Safety and Science Coalition

I. Introduction

On behalf of the Dietary Supplement Safety and Science Coalition ("DSSSC"), these comments are submitted for Food and Drug Administration consideration in establishing the U.S. position on the World Health Organization's ("WHO's") proposal to add several substances to schedules of the 1971 United Nations ("UN") Convention on Psychotropic Substances ("1971 Convention") of the upcoming (March 16-25, 1999) meeting of the UN Commission on Narcotic Drugs ("CND").

The DSSSC is comprised of several businesses in the United States that either manufacture or distribute dietary supplement products containing herbal ephedra (and therefore low levels of naturally occurring ephedrine alkaloids) in the United States and globally. The members of the DSSSC are: The Chemins Company, Inc., Enrich International, Inc., Market America Inc., Metabolife International, Inc., Natural Balance, Inc., Omnitrition International, Inc., and Starlight International, Ltd. The DSSSC was organized to support and develop consistent and responsible standards for the safe consumption of dietary supplements, including the use of science-based approaches when addressing regulatory issues concerning dietary supplements generally, and ephedra in particular.

Specifically of concern to the DSSSC is WHO's Expert Committee on Drug Dependence's ("Committee's") misguided recommendation that the UN add ephedrine to Schedule IV of the 1971

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Convention.[1] The DSSSC strongly objects to the WHO's recommendation generally, and objects particularly if it applies to herbal ephedra products.

This recommendation, and the proposed scheduling, are based upon little or no scientific evidence. The DSSSC believes the factual record is inconclusive with regard to ephedrine, and completely devoid of support with regard to dietary supplement products that contain herbal ephedra. No apparent distinction has been made in the recommendation between ephedrine and herbal ephedra, despite significant differences in the potential for abuse or misuse of the substances. Herbal ephedra has been consumed safely and beneficially in traditional herbal products for more than 5000 years in China, and for centuries in other countries. Today, herbal ephedra is widely and beneficially used in the United States and throughout the world in lawful food and dietary supplement products.

The DSSSC therefore believes that the U.S. should oppose this recommendation and vote against the scheduling of herbal ephedra. A recommendation in favor of scheduling would act to the detriment of consumers who purchase lawful food and dietary supplement products that contain herbal ephedra, and the many companies that manufacture and produce such products. In fact, the U.S. Small Business Administration has emphasized in comments to the FDA the importance of this marketplace.[2] Millions of Americans consume dietary supplements containing herbal ephedra every year and several hundred thousand small businesses are involved in the manufacture, distribution, and sale of these products.

II. Overview of the DSSSC's Position

The DSSSC opposes adding ephedrine to any schedule of the 1971 Convention. The 1971 Convention focuses on the risks associated with the potential for dependence and abuse of a substance and sets forth specific criteria required to justify scheduling as a controlled substance. There is little evidence, however, that ephedrine itself has been abused (*i.e.*, that it produces a state of dependence and mood alteration sufficient to create a public health concern). In fact, the WHO report cited in the January 11, 1999 Federal Register notice indicates that the illicit traffic in ephedrine is "presumably associated" with abuse; evidence of an international problem of dependence and addiction is lacking, particularly in the United States. Thus, it is clear that ephedrine does not satisfy the requirements under the 1971 Convention to warrant international scheduling as a controlled substance. Furthermore, the United States Congress has addressed ephedrine and determined that the substance should be regulated as a "listed chemical" and not a controlled substance. Therefore, the United States representatives to the CND should adhere to the policies set forth by Congress and oppose the proposed scheduling of ephedrine.

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[1] In addition to the substantive issues raised herein, the DSSSC believes the procedures implemented by the WHO failed to comply with WHO guidelines and general principles of equity and fairness. The WHO recommended the scheduling of ephedrine without providing interested parties with its final report on this issue. The WHO also failed to have appropriate expert committees review the ephedrine scheduling proposal prior to initiating the scheduling process. Although the WHO is allegedly committed to ensuring the principles of openness and transparency, these principles have been abandoned in the instant case. The DSSSC believes the U.S. should consider the flaws in the WHO's procedural mechanisms as part of its evaluation of the ephedrine scheduling decision.

[2] See Comments from the Small Business Administration to FDA regarding FDA's proposed rule for dietary supplements containing ephedrine alkaloids. (February 3, 1998)(Attachment A).

Importantly, however, even if ephedrine is scheduled, the DSSSC urges the United States to vote to exclude herbal ephedra and dietary supplement products that contain herbal ephedra from any restrictions imposed on pure ephedrine. There is no credible evidence of abuse of herbal ephedra or dietary supplement products that contain herbal ephedra. Herbal ephedra does not behave like pure ephedrine when ingested and has weaker effects. In addition, dietary supplement products are compounded in such a way that they present only a negligible risk, if any, of misuse. There is simply no evidence that herbal ephedra produces a state of dependence or addiction, particularly when present in low levels in dietary supplement products. Herbal ephedra and products containing herbal ephedra meet none of the criteria required for consideration of scheduling under the 1971 Convention. Consequently, herbal ephedra should be exempted from any scheduling, regardless of the imposition of any restrictions that may be placed on pure ephedrine.

The WHO's concern regarding ephedrine appears to focus on the ingredient's potential use as a precursor in the manufacture of methamphetamines, rather than its abuse potential. The WHO, however, has failed to make the legally required distinction between precursor use and abuse. While the 1971 Convention focuses on the risks associated with scheduled substances themselves, the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances ("1988 Convention") was enacted to address the illicit production of, and traffic in, narcotic drugs. Thus, the 1988 Convention, not the 1971 Convention, is the only proper mechanism designed to address these precursor concerns. The potential use of a substance as a precursor ingredient should be irrelevant to the decision regarding scheduling under the 1971 Convention.

In any event, concerns regarding the precursor use of ephedrine have been addressed; ephedrine is included in the 1988 Convention and is subject to extensive controls arising from its precursor status. Sufficient controls already exist in the U.S. to handle any potential problems involving the use of ephedrine as a precursor as the substance is already a "listed chemical" under the Controlled Substances Act.

Even if potential precursor use is erroneously considered in the CND's scheduling decision, little or no evidence indicates that herbal ephedra, or the products in which it is contained, are used as precursors in the illicit manufacture of methamphetamines. Although the Drug Enforcement Administration ("DEA") alleges that there are instances where herbal ephedra was seized as a potential precursor in the production of methamphetamines, this data is controversial and highly suspect. DEA evidence was seized during routine enforcement actions, without accurate record-keeping or documentation sufficient to support worldwide regulatory action. There is no evidence regarding the context in which herbal ephedra was used, and most importantly, there is no documented evidence regarding the form of the herbal ephedra seized. DEA reports fail to distinguish between bulk ephedra and dietary supplement products that contain ephedra and numerous other ingredients. In fact, it now appears that at most, only one instance identified by DEA involved dietary supplement products that contain ephedra – and even this one incident is subject to significant dispute. There have been no confirmed incidents where dietary supplements that contain herbal ephedra have been used to produce methamphetamines. The DEA's questionable data clearly should not form the basis for the U.S. to conclude that herbal ephedra is subject to abuse and therefore should not lead to the scheduling of herbal ephedra as a controlled substance.

III. Ephedrine, and Especially Herbal Ephedra, Should Not be Scheduled Internationally as There Exists Little or No Evidence of Abuse

A. Criteria for Scheduling under the 1971 Convention

There is no satisfactory basis for the findings required, under Article 2, paragraph 4 of the 1971 Convention, to justify scheduling herbal ephedra as a controlled substance. Paragraph 4 states:

> 4. If the World Health Organization finds:
> (a) That the substance has the capacity to produce
> (i)(1) a state of dependence, and
> (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking behavior or perception or mood, and
> (b) that there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control,
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> the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of this assessment. (emphasis added).

B. There is No Significant Evidence of Abuse of Herbal Ephedra

Although some countries have reported past or present abuse of ephedrine, these reports primarily focus on synthetic and/or pure ephedrine single ingredient products. There is little or no evidence that multi-ingredient ephedrine, herbal ephedra, or dietary supplements containing herbal ephedra are subject to abuse.

Regardless of the findings regarding ephedrine, herbal ephedra, due to significant distinctions from ephedrine, meets none of the criteria required for it to be considered for scheduling under the 1971 Convention. In order for herbal ephedra to be scheduled under the 1971 Convention, it must be determined that the substance is (1) capable of producing a state of dependence; (2) capable of producing central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking behavior or perception or mood; and (3) likely to be abused so as to constitute a public health and social problem. The WHO has failed to set forth adequate evidence in support of any of these criteria. There is no evidence that dietary supplements containing herbal ephedra produce a state of dependence, nor is there any evidence of widespread addiction to such products.[3] Furthermore, dietary supplement products containing herbal ephedra have not been known to cause hallucinations or disturbances in motor function. In

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[3] Such products do not produce a state of "euphoria" and have no functional resemblance to currently controlled substances.

fact, there is absolutely no mention of abuse of herbal ephedra in DEA's April 17, 1998 comments to FDA regarding abuse and trafficking data for ephedrine.

The lack of significant evidence of abuse of herbal ephedra and products containing herbal ephedra is linked in part to the fact that herbal ephedra does not behave like pure ephedrine when ingested and thus has weaker effects. The differences between herbal ephedra and pure ephedrine are believed to be due to (1) the slower absorption of ephedrine alkaloids from herbal ephedra than from pure ephedrine, and (2) the presence of other constituents in herbal ephedra that may counter the effects of the ephedrine itself. The WHO itself has acknowledged the distinction between ephedrine and herbal ephedra. The WHO noted that "when abuse exists, it seems to involve ephedrine single entity products."[4]

Given the lack of an abuse problem for herbal ephedra, there is no basis for concluding that herbal ephedra constitutes a public health and social problem justifying scheduling according to the 1971 Convention. Consequently, herbal ephedra and foods and dietary supplements that contain herbal ephedra should be exempted from scheduling even if ephedrine is added to any schedule under that Convention.

C. There is No Evidence of an International Problem Involving the Abuse of Ephedrine or Herbal Ephedra

In its Critical Review Document on ephedrine, the WHO admitted the difficulty involved with assessing the actual level of ephedrine abuse due to the "long history of generalized safe use of the ephedrine alkaloids in OTC preparations."[5] The WHO reported that ephedrine is available for medical use in forty-six countries around the world, yet alleged that only twelve countries reported "past or present abuse or illicit traffic in ephedrine presumably associated with its abuse."[6]

Upon careful review, however, it appears as if only two countries reported ephedrine "abuse" - and no countries provided confirmed evidence of "abuse" of dietary supplement products that contain herbal ephedra. A review of the responses of these twelve countries in the WHO's Critical Review Document therefore reveals that the information the countries provided regarding the use of ephedrine within their borders does not justify scheduling ephedrine, herbal ephedra, or dietary supplement products containing herbal ephedra as controlled substances according to the requirements set forth in Article 2, paragraph 4 of the 1971 Convention.

Of the twelve countries cited by the WHO in its recommendation:

- Belgium indicated that the "level of abuse does not justify controlling ephedrine as a narcotic or psychotropic drug";[7]

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4 64 Fed. Reg. 1629, 1630 (Jan. 11, 1999) (emphasis added). The WHO also noted that in the United States only, there is some evidence that combination products containing ephedrine have also been abused.

5 WHO Critical Review Document on Ephedrine, Annex 2 (Page 9).

6 64 Fed. Reg. 1629, 1630 (Jan. 11, 1999).

7 WHO Critical Review Document on Ephedrine, Annex 2 (page 8).

- Three countries (China, Germany, and the Sudan) reported to the WHO that past abuse ceased after domestic regulations addressing ephedrine were enacted. These countries no longer experience ephedrine abuse problems;
- Three countries (Finland, France, and Thailand) reported only "a few" cases of ephedrine abuse;
- One country (Burkina Faso) provided no information on ephedrine abuse;
- One country (Ireland) reported "abuse" of ephedrine, but used that term to describe the substances' misuse as a precursor for methamphetamines;
- One country (Slovakia) described "a few cases of misuse," not abuse;
- Only two countries (the United States and Costa Rica) reported ephedrine abuse, and only the United States mentioned potential abuse of ephedrine contained in herbal preparations. As noted herein, however, there is no evidence of "abuse" of dietary supplement products that contain herbal ephedra in this country.

It is clear that the overwhelming majority of the forty-six countries in which ephedrine is available for legitimate purposes indicate no ephedrine abuse problem. Of the twelve countries that the WHO reports indicate some type of abuse problem, three countries state no current abuse problem exists, one country flatly rejects the need to address any abuse problems with scheduling, and one country provided no information at all. While five countries report a few cases of abuse, it is unclear even for these countries if the term "abuse" is being used correctly. Only one country other than the United States reported abuse of ephedrine. International scheduling of ephedrine is unfounded based on the reports of only two countries of any current ephedrine abuse problems at any significant levels. Scheduling of herbal ephedra or dietary supplements containing herbal ephedra is even less justified in light of the fact that only the United States even mentioned these products, and evidence of abuse of these products is lacking.

D. There is Little Evidence of Use of Herbal Ephedra as a Precursor in the Illicit Manufacture of Methamphetamines

As an initial matter, the potential use of ephedrine or herbal ephedra as a precursor ingredient should be irrelevant with regard to deciding whether to schedule a substance under the 1971 Convention. Nevertheless, there is little or no evidence that herbal ephedra or dietary supplements containing herbal ephedra have been successfully used as a precursor for illicit drug production. Pure or synthetic ephedrine is the substance typically used to manufacture methamphetamines and similar controlled substances. In contrast, it is expensive and chemically difficult to use herbal ephedra or dietary supplements containing herbal ephedra (and therefore low levels of ephedrine alkaloids) to manufacture methamphetamines. In fact, it is virtually impossible to convert dietary supplements containing herbal ephedra to produce methamphetamines using the DEA "street method" published in The Journal of Forensic Sciences, Vol. 40, no. 4, July 1995.[8] This is due to the (1) relatively small concentration of ephedrine generally found in herbal ephedra and products containing herbal ephedra, (2) the large quantity of a variety of solvents that would be needed to extract ephedrine from herbal ephedra, and (3) the expense, scientific complications, and inconvenience of this process.

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[8] See April 8, 1998 report from Hauser Laboratories Services (Attachment B)("Based on our analysis, it does not appear that this published method can be used to make methamphetamines....").

1. Using Dietary Supplements Containing Herbal Ephedra as a Precursor is Not Chemically Feasible

There is ample evidence that it is not chemically feasible to use dietary supplements containing herbal ephedra to produce methamphetamines. A recent attempt by a well-respected scientific lab to make methamphetamines from dietary supplements containing herbal ephedra did not succeed in that effort; no methamphetamine was produced when using dietary supplement products containing ephedrine alkaloids.[9] The complex matrix of herbs and other ingredients present in this type of dietary supplement is not conducive to easy conversion to produce pure ephedrine, which in turn makes conversion of the ephedrine into methamphetamines or other controlled substances difficult, if not impossible.

2. The Costs of Synthesizing Methamphetamines from Dietary Supplement Products Containing Herbal Ephedra are Prohibitive

As noted, the use of dietary supplement products that contain herbal ephedra to produce methamphetamines is not chemically feasible. Even if such use was chemically feasible, dietary supplements that contain herbal ephedra are not likely to be used for their ephedrine content to make methamphetamines due to the relative high cost of these products (even if purchased on a volume discount basis) and the relatively low amount of ephedrine alkaloids in each bottle of supplements.

The economic viability of using a substance to produce methamphetamines or other controlled substances should be considered when evaluating whether a substance should be scheduled. For instance, the Committee noted that for one plant-based ingredient under review, the introduction of the ingredient into the illicit market place was "not economically viable either by synthesis or extraction from plant material."[10] Similarly, in the instant case, it would not be economically viable to utilize herbal ephedra dietary supplement products to synthesize ephedrine and methamphetamines. Producing one kilogram of illicit methamphetamines from herbal ephedra itself would require 2000 kilograms of solvents to extract the ephedrine from 200 kilograms of raw ephedra herb. A 3000 liter volume container would be required for the process. Using dietary supplements containing herbal ephedra would increase the difficulty and cost of this operation. Accordingly, the prohibitive economic costs associated with converting dietary supplement products that contain ephedra into ephedrine, and subsequently converting the ephedrine into methamphetamines or other controlled substances, must be considered when determining if such products should be regulated and classified.

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9 Id.

10 See e.g. 55 Fed. Reg. 50404 (Dec. 6, 1990) (emphasis added).

3. DEA Data From Methamphetamine Laboratory Seizures Support the Conclusion That Dietary Supplements Containing Herbal Ephedra Are Not Being Used as Precursor Chemicals

DEA has failed to identify a single confirmed instance where dietary supplement products that contain herbal ephedra have been used to produce methamphetamines. While DEA alleges instances of seizures of herbal ephedra at clandestine drug laboratories since 1993, DEA's allegation appears to have no relevance to dietary supplement products that contain ephedra. According to a DEA report from May, 1997, DEA has documented instances where "ephedra plant materials or extracts of ephedra have also been used as a starting material for the clandestine preparation of methamphetamine."[11] DEA, however, has failed to acknowledge the critical distinction between ephedra plant materials and dietary supplement products that contain ephedra. Of the instances where herbal ephedra was allegedly used as a precursor, none of these instances clearly involve dietary supplement products that contain ephedra.[12]

The absence of evidence supporting the use of dietary supplement products that contain herbal ephedra to synthesize methamphetamines is to be expected. The procedure to synthesize ephedrine, and subsequently produce methamphetamines, is complex, if not impossible, when the starting material is ephedra plant materials or diluted extracts of ephedra plant materials. Importantly, however, the level of complexity increases exponentially when the starting material is a dietary supplement product that contains herbal ephedra, and the complexity further increases as other natural ingredients are combined with herbal ephedra. Dietary supplement products that contain ephedra typically contain numerous other ingredients, including stabilizers, fillers, other herbs, vitamins, etc. Extracting pure ephedrine from a multi-ingredient dietary supplement product is an arduous, expensive, and time-consuming task that effectively removes such products from use as precursor materials. DEA's assessment that ephedra could be used "experimentally" to make methamphetamines was based on DEA's use of the raw herb ephedra, not dietary supplements containing a number of ingredients.[13]

Furthermore, DEA, in a recent proposed rule to exempt certain chemical mixtures that contain regulated chemicals under the 1993 Domestic Chemical Diversion Control Act, acknowledged that dietary supplements were rarely encountered at illicit laboratories. According to DEA, the "frequency with which these products [dietary supplements containing herbal ephedra] are encountered is small."[14] In its proposed rule, DEA noted the difficulty of using either (1) dietary supplements containing herbal ephedra at low levels or (2) multiple ingredient products containing higher concentrations of ephedrine alkaloids, in the illicit production of methamphetamines.[15]

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11 Department of Justice ("DOJ"), Ephedra: A Potential Precursor for D-Methamphetamine Production (May 1997)("DOJ Paper"), Page 1.

12 Four instances cited by DEA refer to the seizure of raw materials such as raw herbal ephedra. In one instance, the DEA report refers to the seizure of "ephedra tablets originating from a pharmaceutical company." It therefore does not appear as if any of the seizures involved dietary supplement products that contain herbal ephedra. There is also no evidence that the seized materials were used to produce methamphetamines. Id.

13 Id.

14 See 63 Fed. Reg. 49506, 49507 (September 16, 1998).

15 Id. at 49509.

Consequently, there is no credible evidence that herbal ephedra, and in particular, dietary supplements containing herbal ephedra, will be diverted to manufacture methamphetamines. Using supplements to extract ephedrine for the manufacture of methamphetamines is neither practical nor chemically feasible.

IV. The U.S. Congress, DEA, and FDA Have Never Determined That Ephedrine Presents a Potential for Abuse Requiring A Ban On Over-The-Counter Availability

A. Federal Laws and Regulations

The laws and regulations currently in place in the U.S. addressing ephedrine or herbal ephedra follow the provisions set forth in the 1988 Convention by focusing on the potential of substances as precursors in the manufacture of methamphetamines. The proposal to add ephedrine to Schedule IV of the 1971 Convention is the type of controlled substance scheduling decision the U.S. government has intentionally avoided due to the necessity of ensuring consumer access to effective OTC drug and dietary supplement products containing ephedrine or herbal ephedra. The thrust of U.S. laws that address ephedrine or herbal ephedra involve diversion, not abuse. Problems with diversion of ephedrine, which do not relate to herbal ephedra, have already been addressed domestically through the registration controls placed on these products at state and federal levels and internationally through the 1988 Convention. Broad based restrictions that would result from scheduling under the 1971 Convention are unwarranted, unjustified, and devoid of factual support.

B. Congress Evaluated Ephedrine - and Opted to Regulate it as a "Listed Chemical" and not a Controlled Substance

Ephedrine is not a controlled substance in the United States under the federal Controlled Substances Act ("CSA"). Ephedrine is, however, a "listed chemical" under that law and the three Acts that have amended the CSA (which were intended to prevent diversion of substances into the illicit market). The Chemical Diversion Trafficking Act of 1988, the Domestic Chemical Diversion Control Act of 1993, and the Comprehensive Methamphetamine Control Act of 1996 amended the CSA and provided the DEA with significant powers to address the diversion of ephedrine or herbal ephedra as a precursor in illicit methamphetamine production. Congress did not make products containing ephedrine or herbal ephedra subject to a controlled substances schedule. Congress focused on the diversion of ephedrine as a precursor to the manufacture of methamphetamines--not on the risks of direct abuse of ephedrine or herbal ephedra. In addition, several states have developed regulations addressing the diversion of ephedrine that also follow the U.S. federal framework.

Ephedrine is a List I chemical under the CSA.[16] A List I chemical is defined as "a chemical specified by regulation of the Attorney General as a chemical that is used in manufacturing a controlled substance in violation of this subchapter and is important to the manufacture of the controlled substances... ."[17] Because ephedrine is a List I chemical, its manufacture and distribution

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16 Section 102(34)(C) of the CSA, 21 U.S.C. § 802(34)(C).

17 Id.

is regulated by the DEA. Most persons who manufacture or distribute a List I chemical are required to register annually with the United States Attorney General. Also, each regulated person who engages in a regulated transaction involving a "listed chemical" must keep a record of the transaction for two years after the date of the transaction.

If ephedrine abuse presented a significant problem in the United States, FDA, DEA, and Congress would have taken swift regulatory measures to attempt to prevent or curtail this abuse by classifying ephedrine as a controlled substance. As noted, however, ephedrine is not a controlled substance but rather is only a List I chemical. Therefore, when Congress made this determination, it decided that synthetic or single entity ephedrine may be implicated in the manufacture of a controlled substance (*i.e.*, ephedrine may be a "listed chemical"), but did not classify ephedrine as a controlled substance.[18]

The proposed scheduling of ephedrine as a Schedule IV controlled substance by the UN could require the implementation of regulations in the U.S. to fully incorporate the provisions of the 1971 Convention, including requiring medical prescriptions to dispense ephedrine as well as licenses for manufacturers, distributors and retailers of ephedrine products. These regulatory requirements contradict the U.S. Congress's intent, reflected in the regulation of ephedrine as a "listed chemical" only, to maintain consumer access to ephedrine products without prescription. The international scheduling requirements would erode the ability of the U.S. to regulate a therapeutic and beneficial substance in the most effective and appropriate manner for its use in this country.

Due to the absence of evidence to support the characterization of ephedrine as a controlled substance, dietary supplement products that contain ephedra should clearly be outside the scope of controlled substance regulation. In fact, even the DEA has confirmed that dietary supplement products that contain herbal ephedra are distinguishable from bulk ephedrine and drug products that contain ephedrine. DEA has proposed the exemption of "chemical mixtures" that contain ephedra from DEA regulatory requirements.[19] DEA indicated that dietary supplement products that contain herbal ephedra may be formulated in such a way that they cannot be easily used in the illicit production of a controlled substance, and the ephedrine cannot be readily recovered at doses sufficient to be used for illicit purposes.[20] DEA has therefore acknowledged that the frequency with which dietary supplement products that contain ephedra have been abused is low.

V. Economic and Social Factors Should be Considered in Scheduling Decisions

Under Article 2, paragraph 5 of the 1971 Convention, the CND is to consider economic and social factors, among others, when determining whether to add a substance to any schedule. The U.S. should consider the detrimental impact the proposed scheduling of ephedrine will have on both

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18 Ephedrine is a mild central nervous system stimulant with potency, at normal therapeutic doses, similar to that of caffeine. Caffeine, which is regulated by FDA as a stimulant drug ingredient (see 21 C.F.R. § 340.10), has never even been considered for scheduling as a controlled substance. It is therefore undoubtedly the case that the pharmacological properties of ephedrine, and the potential for abuse, are of a different order of magnitude from those substances currently characterized as controlled substances.

19 63 Fed. Reg. 49506 (September 16, 1998).

20 Id. (DEA proposed an ephedrine concentration limit, which is under review, to ensure compliance with these standards.)

consumers and businesses in this country. The proposed scheduling of ephedrine would restrict consumer access to products containing pure or synthetic ephedrine, such as bronchodilators, that FDA has concluded are safe for over-the-counter use when properly labeled and taken as directed.[21] Furthermore, over five million people consume dietary supplement products containing ephedra in the United States each year according to conservative estimates. If ephedrine is added to Schedule IV of the 1971 Convention, these millions of consumers would be prohibited from purchasing over-the-counter dietary supplements that contain ephedra; prescriptions from licensed health care practitioners would be required to obtain such products.

The impact of the scheduling of ephedrine on U.S. businesses that manufacture or distribute ephedrine and herbal ephedra-containing products would be severe as well. FDA has estimated that there are between 200 and 5,000 products containing ephedrine alkaloids on the market.[22] According to estimates by the dietary supplement industry and the U.S. Small Business Administration, a significant number of the several hundred thousand businesses that would be impacted by the proposed scheduling are "small" businesses.[23]

VI. If Further Controls Would be Needed (and They are Not), the 1988 Convention is the Proper Mechanism to Address Concerns Regarding the Use of Ephedrine or Herbal Ephedra as Precursors in the Manufacture of Illicit Drugs

A. 1988 Convention Overview

Ephedrine is listed in Table 1 of the 1988 Convention as a precursor chemical. The 1988 Convention was enacted to reinforce and supplement the 1971 Convention to more effectively address the illicit production of, demand for, and traffic in narcotic drugs and psychotropic substances.[24] The 1971 Convention, on the other hand, focuses on the risks associated with the scheduled substances themselves. As described in more detail above (see Section III), the abuse risks of ephedrine or herbal ephedra are not significant enough to warrant scheduling.

The 1988 Convention sets forth a number of measures to be adopted by the Parties to the Convention ("Parties") to prevent the diversion of listed substances, including, among others:

- establishing a system to monitor the international trade of listed substances;
- authority to seize listed substances if evidence shows they are being used as a precursor;
- labeling and documentation requirements for imports and exports of listed substances;
- record-keeping requirements for imports and exports of listed substances.[25]

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21 See 21 C.F.R. Parts 341.16 ("Bronchodilator active ingredients.").

22 62 Fed. Reg. 30,678, 30,710 (June 4, 1997).

23 See Comments from the Small Business Administration to FDA regarding FDA's proposed rule for dietary supplements containing ephedrine alkaloids (February 3, 1998)(See Attachment A).

24 See 1988 Convention, Preamble and Article 2.

25 See 1988 Convention, Article 12 (9)(a) -(e).

Thus, new concerns regarding the diversion of ephedrine for the illicit manufacture of drugs or psychotropic substances could be fully addressed by the 1988 Convention. No problem of this type exists for dietary supplements containing herbal ephedra. Parties are continuing to take action to ensure that their domestic policies fully incorporate the provisions of the 1988 Convention. The United States, for example, enacted the 1993 Domestic Chemical Diversion Control Act ("DCDCA") in part to address domestic regulations that were inconsistent with the requirements of the 1988 Convention. Moreover, the DEA has in fact recently proposed a regulation seeking to implement the DCDCA in an effort to prevent the diversion of chemical mixtures containing listed substances.[26]

B. Potential Conflict Between the 1971 Convention and the 1988 Convention

Adding ephedrine to Schedule IV of the 1971 Convention, when it is already listed in and regulated by the 1988 Convention, will create confusion among the Parties and make enforcement of any restrictions on ephedrine troublesome. It is unclear whether the regulatory requirements (such as labeling and recordkeeping for imports and exports) and enforcement tools (such as the authority to seize listed substances used as precursors) applicable to ephedrine as a chemical listed under the 1988 Convention would still apply if the substance is scheduled as a controlled substance under the 1988 Convention. It is also unclear whether actions in compliance with one of the Conventions would satisfy the requirements of the other, or if separate record keeping and monitoring systems, for example, would be necessary under each Convention. As the Committee pointed out in its recommendation, the overlapping jurisdictions of the 1971 Convention and the 1988 Convention would likely make "full effective international regulations of ephedrine difficult."[27]

Furthermore, the Committee stated that interpretation of these two Conventions by the International Narcotic Control Board and WHO is needed.[28] A formal interpretation, however, has not been promulgated. Accordingly, it is not prudent to add additional international regulations when the jurisdiction of the proposed regulations is in question. The United States should not support international regulations when the domestic regulatory impact of these regulations is unclear due to the confusion regarding the jurisdiction of the Conventions. At a minimum, the DSSSC feels that the United States should demand that the jurisdiction of the 1971 and 1988 Conventions be clarified before considering the Committee's recommendation on this matter.

VII. The United States Can Exclude Herbal Ephedra Pursuant to Provisions in the 1971 Convention

To prevent disruption of the current U.S. regulatory system, preserve sovereignty, and avoid international pressure, the U.S. should vote against any scheduling of ephedrine and particularly herbal ephedra under the 1971 Convention. However, there are several means by which the U.S. could potentially exclude ephedra and dietary supplements containing ephedra from any restrictions imposed on ephedrine, pursuant to provisions of the 1971 Convention.

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26 63 Fed. Reg. 49506 (September 16, 1998).

27 64 Fed.Reg. 1629, 1630 (January 11, 1999).

28 Id.

A. If the UN Erroneously Schedules Ephedrine, the Will of Congress Should be Followed Domestically and the U.S. Should Exempt Itself from Implementing This Regulation

Under Article 3, paragraph 2 of the 1971 Convention, a preparation may be exempted from certain control measures if it is compounded in such a way that it presents little or no risk of abuse such that the substance cannot be recovered from the preparation in a quantity liable for abuse. The DSSSC believes that dietary supplements containing herbal ephedra are compounded in such a way that they cannot be easily and practically used in the illicit manufacture of a controlled substance (if they can be used at all) and thus present at most a negligible risk of being used as a precursor chemical. Furthermore, as explained throughout this document, such preparations pose no risk of "abuse."

B. Parties May Elect Not to Apply Certain Provisions of the Convention

In the alternative, under Article 2, paragraph 7 of the 1971 Convention, a party may decline to implement certain provisions in the applicable schedule upon notice to the Secretary-General of "exceptional circumstances." The DSSSC believes that based on the safe and beneficial use of dietary supplements containing herbal ephedra and the unfounded, extreme restrictions that would result from including herbal ephedra in any scheduling of ephedrine, "exceptional circumstances" would demand that the United States notify the Secretary-General that it is not in a position to implement all provisions of any scheduling imposed on ephedrine.

VIII. Conclusion

Scheduling of ephedrine or herbal ephedra under the 1971 Convention is misguided and unnecessary. The factual record for ephedrine does not support the conclusion that the substance should be scheduled as a controlled substance under the 1971 Convention. There is insufficient evidence of widespread abuse of ephedrine in the U.S. or globally to justify its international regulation as a controlled substance. While forty-six countries reported to the WHO that ephedrine is used therapeutically for medical purposes, only the U.S. and Costa Rica reported any ephedrine "abuse." As noted, however, the term "abuse" appears to have been misused.

In any event, sufficient controls are currently available in the U.S. and throughout the world to address any problems associated with ephedrine in an appropriate manner. The 1988 Convention provides sufficient mechanisms to control ephedrine use, and in the U.S. ephedrine is regulated as a "listed chemical" subject to significant regulatory controls.

If, however, ephedrine is added to any schedule of the 1971 Convention, herbal ephedra and dietary supplements containing herbal ephedra should not be scheduled. There is no evidence that herbal ephedra produces a state of dependence or addiction. Herbal ephedra and dietary supplements containing herbal ephedra are simply not "abused." Therefore, herbal ephedra and dietary supplements containing herbal ephedra do not meet the criteria required for scheduling under the 1971 Convention, and should be excluded from any scheduling that may be imposed on ephedrine.

Importantly, potential use of a substance of as a precursor should not be considered in a scheduling decision under the 1971 Convention, the purpose of which is to address the abuse potential of a substance. The 1988 Convention is the proper means to address precursor use, and this Convention already includes ephedrine as a regulated substance. Nevertheless, even if potential precursor use is mistakenly considered in the decision to schedule ephedrine under the 1971 Convention, there is little credible evidence indicating that herbal ephedra, particularly when present in low levels in dietary supplement products, is used as a precursor in the illicit manufacture of methamphetamines. DEA's suspect data regarding the alleged seizure of herbal ephedra products as potential precursor material should not form the basis for the U.S. to determine that herbal ephedra is in fact successfully used in the manufacture of methamphetamines. The evidence indicates that using herbal ephedra and dietary supplements containing herbal ephedra to synthesize methamphetamines is chemically difficult, if not impossible. Furthermore, the U.S. has a regulatory scheme in place to adequately address any legitimate concerns regarding the precursor use of a substance. Consequently, unfounded concerns regarding the use of herbal ephedra in the manufacture of methamphetamines does not justify scheduling the substance under the 1971 Convention.

In addition to the scientific factors supporting the exclusion of herbal ephedra, the CND may take into consideration economic, social, legal, administrative, and other relevant factors when determining whether to add ephedrine to Schedule IV of the Convention and whether to exclude ephedra from the Schedule. The DSSSC urges the United States to consider the impact of restricting the access of millions of consumers to herbal ephedra and products containing herbal ephedra. The proposed scheduling would have a devastating impact on hundreds of thousands of businesses – the manufacturers, distributors, and retailers of lawful dietary supplement products containing herbal ephedra. The DSSSC believes that the United States should support efforts to distinguish herbal ephedra, and products that contain herbal ephedra, from pure ephedrine. Even if restrictions are imposed upon ephedrine, such restrictions should not be imposed upon herbal ephedra and dietary supplement products that contain herbal ephedra.

Respectfully submitted,

Stuart M. Pape
James R. Prochnow
Daniel A. Kracov

Counsel to the Dietary Supplement Safety
and Science Coalition

ATTACHMENT A

U.S. SMALL BUSINESS ADMINISTRATION
WASHINGTON, D.C. 20416

OFFICE OF CHIEF COUNSEL FOR ADVOCACY

February 3, 1998

Dockets Management Branch
HFA-305
Food and Drug Administration
12410 Parklawn Drive
Room 1-23
Rockville, MD 20857

Re: Initial Regulatory Flexibility Analysis of the Proposed Rule for Dietary Supplements Containing Ephedrine Alkaloids, 62 Fed Reg. 30,678 (June 4, 1997); Docket No. 95N-0304

Dear Dockets Management Clerk:

On June 4, 1997, the Food and Drug Administration (FDA) published a notice of proposed rulemaking concerning the regulation of dietary supplements containing ephedrine alkaloids (from botanical sources rather than pharmaceutical sources). Because of the holiday season and the Office of Advocacy's unexpected participation in pending litigation of agencies' compliance with the Regulatory Flexibility Act (RFA),[1] the Office of Advocacy was not able to file these important comments in a timely fashion.

Under the proposed regulation, a dietary supplement would be considered adulterated if it contains 8 milligrams or more of ephedrine alkaloids per serving, or its labeling suggests or recommends conditions of use that would result in intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. In addition, the new regulation would require that the label of dietary supplements that contain ephedrine alkaloids state the following: 1) "Do not use this product for more than 7 days"; 2) "Taking more than the recommended serving may result in heart attack, stroke, seizure or death"; and 3) other specific warning statements. Finally, the proposed regulation would prohibit: 1) the use of ephedrine alkaloids with ingredients that contain substances like caffeine known to have a stimulant effect; and 2) labeling claims that require long-term intake to achieve the purported effect. This massive regulation is designed to address certain incidents of illness, injury and death purportedly associated with the use of dietary supplement products containing ephedrine alkaloids.

The Office of the Chief Counsel for Advocacy of the U.S. Small Business Administration was created in 1976 to represent the views and interests of small business in federal policy making activities.[2] The Chief Counsel participates in rulemakings when he deems it

[1] Regulatory Flexibility Act, 5 U.S.C. § 601, as amended by the Small Business Regulatory Enforcement Fairness Act, Pub. L. No. 104-121, 110 Stat. 866 (1996).
[2] Pub. L. No. 94-305, 90 Stat. 668 (codified as amended in 15 U.S.C. §§ 634a-g, 637)).

necessary to ensure proper representation of small business interests. In addition to these responsibilities, the Chief Counsel monitors compliance with the Regulatory Flexibility Act (RFA), and works with federal agencies to ensure that their rulemakings demonstrate an analysis of the impact that their decisions will have on small businesses.

In order to get to the argument of whether the FDA has complied with the RFA expeditiously, the Office of Advocacy will assume arguendo that FDA has the statutory authority to promulgate this rule.[3] Upon publishing in the *Federal Register* a proposed rule, §§ 603 and 605(b) of the RFA require that an agency head must either certify that a proposed rule will not have a significant economic impact on a substantial number of small entities, or prepare an initial regulatory flexibility analysis (IRFA). Having determined that the rule would have a significant economic impact, FDA correctly chose the option to perform an IRFA. However, as explained below, FDA has done an inadequate job of analyzing the impact of the regulation on small entities and in identifying and analyzing less burdensome alternatives. In addition, FDA committed several other procedural errors including failing to observe the notice and comment requirements of the Administrative Procedure Act (APA). 5 U.S.C. § 553.

I. Number of Entities Affected

In order to determine the impact of any regulation, an agency must make a reasonable effort to identify the type and number of entities likely to be affected by the regulation. This process of learning about the regulated industry not only helps the agency determine whether to certify a rule for regulatory flexibility purposes, it also helps the agency develop an analysis of impacts and choose appropriate regulatory alternatives that minimize economic burden.

In the instant case, those industries likely to be impacted include distributors (wholesalers and retailers) and manufacturers of ephedrine alkaloids. FDA estimates that there are between 200 and 5,000 products on the market containing ephedrine alkaloids,[4] and, at the end of the proposed rule, FDA estimates that only 80 small businesses will be impacted.[5] This is a curious number because the Office of

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[3] The Dietary Supplement Health and Education Act (DSHEA), Pub. L. No. 103-417, § 2(13), 108 Stat. 4325, 4326 (1994), places specific limits on how FDA can regulate or enforce against dietary supplements FDA believes are unsafe or adulterated. Specifically, DHEA requires the FDA to prove adulteration on a product-by-product basis rather than designate by regulation when a class of dietary supplements containing ephedrine alkaloids are adulterated under the Food, Drug and Cosmetic Act, 21 U.S.C. § 342(f)(1). The Office of Advocacy believes that there is considerable merit to the argument that FDA does not have the authority in the instant rulemaking to designate by regulation that all dietary supplements containing ephedrine alkaloids are adulterated.

[4] 62 Fed. Reg. at 30,710.

[5] 62 Fed. Reg. at 30,712. In reaching its determination on the number of small entities impacted, the agency relied on the estimates appearing in the final rule on nutritional labeling and on survey data. The estimated number of dietary supplement manufacturers in the nutritional labeling rule was between 500 and 850 firms, with 95 percent of those firms classified as small businesses. The proportion of manufacturers producing products containing ephedrine alkaloids was not revealed in the nutritional supplement rule, but two market surveys identified 85 manufacturers and distributors of dietary supplements suspected of containing ephedrine alkaloids. Using the 95 percent proportion from the nutritional labeling rule, the agency arrived at the figure of 80 small firms (95% of 85 firms equals 80

Advocacy received 159 letters from small distributors likely to be impacted directly by the proposed regulation—double the number estimated by FDA. Surely, the letters received by the Office of Advocacy represent a mere fraction of the number actually impacted. The Office of Advocacy is also aware that many ephedra products are sold by tens of thousands of home-based distributorships that are part of multi-level marketing companies. Many of these businesses, although part of a larger parent company, may nevertheless be independently owned and operated and considered to be "small business concerns" under the Small Business Act.[6]

FDA should develop an outreach strategy to obtain more reliable industry data. Industry trade associations are typically a good starting place. In fact, FDA is obligated under § 609(a) of the RFA to engage in outreach efforts to ensure small business participation in the rulemaking process. In other words, § 609 requires agencies to do more than publish a notice of proposed rulemaking in the *Federal Register*, and may include such strategies as direct notification of interested small entities.

II. Cost-Benefit Analysis

The discussion below paints a clear picture of FDA's failure to comply with the RFA. The heart of the RFA is the requirement for an economic impact analysis to determine the impact on small businesses and the requirement for proposing and analyzing less burdensome regulatory alternatives and explicitly stating the reasons for accepting or rejecting the alternatives presented. When an agency relies on faulty data in its analysis—as in the instant case—the result is a flawed analysis with inflated benefits claims and underestimated industry costs.

Based on the information gleaned directly from the docket and the proposed rule, and from the accounts of industry experts, the Office of Advocacy opines that the benefits of the instant proposed rule are much lower than FDA's estimates—by FDA's own admission, possibly even zero. Simply, FDA's data do not demonstrate the need for the regulation. Having acknowledged that the rule will have a significant economic impact on a substantial number of small entities, FDA had a duty to analyze accurately the impact of its proposal and design appropriate regulatory alternatives.

A. Scientific Evidence?

FDA cites as the reason for its proposed rule, "serious illnesses and injuries, including multiple deaths, associated with the use of dietary supplement products that contain ephedrine alkaloids and the agency's investigations and analyses of these illnesses and injuries." 62 Fed. Reg. at 30,678. FDA, however, relies on adverse event reports (AERs) to suffice as evidence of the need for the regulation.

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firms). The source and date of the market data is not clear. Moreover, FDA assumes that the estimates in the nutritional labeling final rule regarding the number of manufacturers corresponds to the information collected in the market data with regard to manufacturers and distributors.

[6] *See* 15 U.S.C. § 632(a)(1).

First, by its own admission, FDA states that AERs are not a reliable source of data upon which to draw conclusions regarding the health effects of a particular substance. In the proposed rule, FDA acknowledges that:

> "a possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure," and that "many of the AERs did not provide enough information to adequately evaluate . . . [causality]." 62 Fed. Reg. at 30,689-90.

In numerous other instances within the docket the agency cites the unreliability of AERs. For instance, Docket Vols. 190 and 263 which catalogue the AER reports contain certain disclaimers:

> The evaluation of data in [a] passive surveillance reporting system . . . is limited by several recognized factors:
>
> - Because reporting is voluntary, adverse events may occur which are not reported, and are therefore not in SNAEMS [Office of Special Nutritionals Adverse Event Monitoring System]
> - A single case may be reported more than once, inflating the number of reports in the system . . .
> - There is no certainty that an adverse event can be attributed to a particular product, or ingredient in a product
> - An event may be related to or modified by an underlying disease or condition, to other products which are taken concurrently, or the event may have occurred by chance at the same time the suspected product was taken
> - Accumulated case reports cannot be used to calculate incidents or estimates of product risk. They must be carefully interpreted as reporting rates, and not as occurrence or incidence rates. The length of time that a product has been marketed, the market share, experience and sophistication of the population using the product or evaluation of the adverse event, publicity about an adverse reaction, and regulatory actions are all factors that influence the probability that an adverse event will be reported. Comparisons of product safety cannot be directly obtained from these data.

With regard to the last disclaimer on accumulated case reports cited above, FDA ignores its own warning. That is, FDA states that between 1993 and 1996 it received "a rapidly escalating number of AERs associated with the use of dietary supplements, some that contained ephedrine alkaloids, some that did not." 62 Fed. Reg. at 30,680. Based on this "analysis," the agency concludes that increased AERs translate to increased risk to the general population. FDA, however, does not attempt to offer any other explanation for increased reports. Increased exposure is not the same as increased risk. For instance, increases in the number of people using such products could be a factor in increased reports. FDA's flawed "analysis" is misleading for reasons already acknowledged by FDA, and for other common sense reasons outlined below.

FDA never establishes a baseline for its analysis. In other words, FDA does not provide any information on the percentage of individuals in whom the purported side effects would occur naturally or randomly. General symptoms like increased heart rate, elevated blood pressure, nervousness or insomnia may occur after drinking two cups of coffee, taking an over-the-counter (OTC) product like Dexatrim[7] or Actifed[8], listening to a screaming toddler on an airplane, or a bad day at work. It would be easier to establish a causal relationship, for instance, if a higher than normal percentage of the population developed less common symptoms or diseases like Creutzfeldt-Jakob disease (a human variant of "mad cow disease") after consuming contaminated beef.

Also, the AERs contained in volumes 190 and 263 of the docket are inherently inconclusive and lacking in vital data, and no reasonable person could draw any conclusion regarding causality from the information provided—especially the conclusion that ephedrine alkaloids were the cause of the reported illness. There is no way to truly determine, for instance whether a particular reaction, if in fact caused by a dietary supplement, was due to a deliberate overdose or preexisting medical condition. Based on information assembled by the industry (at great expense and effort), out of 920 reports[9], 662 (approximately 72%) of the AERs lack medical records, and over 123 (approximately 13%) AERs list products for which there is no indication that the product contains any ephedrine alkaloids. In total, the industry experts cited 784 (approximately 85%) AERs that were lacking vital data.[10]

In addition to the lack of data in the AER reports, industry experts who carefully reviewed each AER in the docket discovered some astonishingly peculiar and irrelevant information. The experts found cases where adverse events occurred absent the use of an ephedra product, cases where no adverse effect was listed, events medically unrelated to ephedrine ingestion, and other bizarre reports like a case where a patient became pregnant though using an implanted birth control device.[11] These reports have no rational relationship to the safety or efficacy of ephedrine alkaloid products. If the industry accounts of the AERs are accurate, then the Office of Advocacy can only conclude that FDA never

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[7] The active ingredient in Dexatrim is phenylpropanolamine (PPA) with a daily recommended dosage of 75-mg. It is an amphetamine-like substance that disrupts hunger signals to the brain. Certain individuals who ingest PPA through weight loss or OTC cold products may experience nervousness, nausea, insomnia, headaches and elevated blood pressure. These warnings are on the product labels, yet FDA is not trying to remove these products from the market because they are unsafe at the recommended doses.

[8] One of the active ingredients in Actifed is pseudoephedrine hydrochloride with a daily recommended dosage not to exceed 240 mg. According to the product label, some people may experience "nervousness, dizziness, or sleeplessness."

[9] The 920 reports should be placed in the context of billions of doses of dietary supplements taken by consumers over the past couple of years. FDA states that they have collected over 125 dietary supplement products labeled as containing a known source of ephedrine alkaloids during the past two years. *See* 62 Fed. Reg. at 30,679. Even if only one billion doses had been taken, it would amount to only .0000009% of doses consumed that resulted in a report. Statistically, speaking, it is very possible that an even higher percentage of the general population would have died or experienced general symptoms resembling those associated with the reported events contained in the AERs.

[10] Starlight's and Nutraceutical's Comments to FDA's Proposed Rule on Dietary Supplements Containing Ephedrine Alkaloids (Vol. I) at 46 (December 2, 1997).

[11] *Id.* at 47-49.

checked or approved the individual reports prior to their inclusion in the docket. In any event, the industry experts concluded that there were "no deaths or serious injuries from consumption of ma huang at levels approaching 25 mg per serving taken four times per day, even for prolonged periods."[12]

Finally, the data and/or studies primarily relied upon by the agency deal with the pharmaceutical equivalent of ma huang (botanical ephedra). FDA states:

> the agency was not able to find definitive evidence to evaluate whether ephedrine alkaloids from botanical sources are metabolized differently than those from pharmaceutical sources, and in the absence of more directly relevant data for dietary supplement products, the agency considered it appropriate to rely on evidence from pharmaceutical sources of single ephedrine alkaloids in assessing the effects of botanical sources. 62 Fed. Reg. at 30,682.

There is an inappropriate leap of logic involved in assuming that botanical sources (ma huang) containing mixtures of ephedrine alkaloids are the same as a single ephedrine alkaloid found in pharmaceutical derivations. There is no evidence, for instance, that botanical and pharmaceutical derivations have the same potency or that they are metabolized in the body the same way.

B. Methodology of FDA's Analysis

Assuming FDA's data were accurate, the agency again departs from requirements of the RFA by failing to explain fully the process of its analysis of benefits. Specifically, the agency's claims regarding lives saved and the elimination of serious injuries are unsubstantiated. Table 6 is used to summarize estimated benefits in terms of risk reduction.[13]

In Table 6, titled, Estimated Value of Annual Risk Reduction From Proposed Actions, FDA lists six columns: 1) Type of adverse event 2) Annual reported cases, 3) Estimated annual cases, 4) Reduction in estimated annual cases, 5) Value of estimated risk reduction per case ($ thousands), and 6) Value of estimated risk reduction ($ millions). The totals for each column are based on the combined number of deaths, serious cardiovascular system events, etc. as they relate to each column.

- The source of the data for annual reported cases in column two is not apparent. FDA states that the annual reported cases are based on the average number of adverse event reports per year between January 1993 and June 1996. The total for this column is 174. If FDA is relying on the misleading and incomplete AERs appearing in the docket, the total for this column should be much lower—maybe even zero. If FDA is relying on some other data source, then that source should be revealed.
- The estimated annual cases in column three—1,110—are based on a number of peculiar assumptions. The agency assumes that 80% of the AERs involving the consumption of dietary supplements suspected of containing ephedrine alkaloids are actually related to the consumption of dietary supplements, that 80% of the

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[12] *Id.* at 50.

[13] Table 6 is reproduced in Appendix B of this document.

supplements involved in the AERs that are related to the consumption of supplements actually contain ephedrine alkaloids,[14] and 10% of adverse events to the dietary supplements are reported. The agency, however, admits that "considerable uncertainty exists with respect to the validity of the assumptions on which this estimate is based." 62 Fed. Reg. at 30,708. FDA provides no information regarding the basis of their assumptions.

- The values of estimated risk reduction per case in column five are based on 1988 data that estimates the value consumers place on reducing risk of: 1) acute CNS and liver or kidney changes, 2) chronic CNS system impairment, and 3) heart disease and stroke. The dollar values were then converted from 1988 to 1996 consumer indices. The values consumers place on reduced risk per case is irrelevant if the risk does not exist. In other words, if there is no proven risk, then there is no risk to reduce and there is no benefit. The same is true for the figures in column six—value of estimated risk reduction—since they rely on the data in columns four and five. Moreover, if column two (which relies on false, misleading and confusing AERs) totals zero, then so does column six.

In the instant case, the faulty data, inappropriate data assumptions, and other serious errors all contributed to the faulty analysis—an analysis that overestimates the benefits and undermines the entire rulemaking.

C. Intake Restrictions

FDA proposes dosage limits by restricting the per serving amount and frequency, and also proposes limits on the duration of use. The agency proposes that 8 mg be the maximum serving/dose for dietary supplements.[15] Products with higher dosage amounts will be considered adulterated under the proposal. However, there is no research or data to support any of the proposed restrictions.

FDA relies on a study of ephedrine in 20 mg per serving dosages to support its 8 mg restriction, but there is a fourfold problem inherent in relying on this data. First, the study does not involve botanical sources of ephedrine alkaloids. Second, the agency does not adequately address how it concluded that 8 mg was an appropriate amount when the study relied on 20 mg dosages. Third, the 20 mg study did not apply to the general population, but to the morbidly obese—who are generally at higher risk for health problems. Fourth, the 20 mg study dealt with testing the effectiveness of the dosage and not its safety. FDA then tries to buttress its 8 mg dosage requirement by referencing postmarketing surveillance data. The agency "[analyzed] the ephedrine alkaloid levels in the small number of available dietary supplement products that consumers who suffered adverse events turned over to the agency."[16] The levels were found to range from 1 to 50 mg per

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[14] The 80% figure was determined by FDA as follows: "the proportion of reported adverse events associated with dietary supplements that involve supplements containing ephedrine alkaloids is probably between 25 and 90 percent. Within this range, FDA believes the most likely value is around 80 percent . . ." (Emphasis added). 62 Fed. Reg. at 30,707.

[15] 62 Fed. Reg. at 30,692-93.

[16] *Id.* at 30,693.

serving. This information does not necessarily support the agency's proposition that doses exceeding 8 mg are harmful because there is no way to know whether there were deliberate overdoses, whether consumers were taking products marketed as substitutes for illegal drugs, whether the reported reactions were related to some other cause, etc.

In addition, the agency admits that, "[g]iven the available evidence, it is difficult to ascertain whether there is a threshold level of ephedrine alkaloids below which the general population and susceptible individuals will not experience serious adverse events."[17] The agency goes on to say that, "[t]he evidence does not exist to establish a safe level."[18] It seems that the converse could also true based on the proposed rule as written. That is, a maximum safe level cannot be determined either. The data presented by the agency does not prove the need for any per serving restriction. In fact, FDA states that "all that can be said concerning the proposed potency limits is that they may reduce the expected number of adverse events by between zero to 80 percent."[19] If the FDA cannot demonstrate the lack of safety of a product, then, given the statutory burden of proof for dietary supplements, there is no basis to regulate the product.

Similar arguments can be made against FDA's proposed frequency and duration restrictions. The agency proposes a label statement prohibiting claims related to weight loss and concomitantly placing a 7-day limit on the use of ephedrine alkaloids with a maximum daily intake of 24 mg (three 8 mg doses per day). Many of the affected products are for weight loss and would exceed the proposed requirements—particularly the duration requirement. In fact, if a distributor stocks mainly weight loss supplements, then that distributor surely would go out of business because weight loss products must generally be taken for a longer period in order to be effective. To avoid unnecessary burden on the industry, thoughtful attention must be given regarding the basis for the duration requirement.

The agency states that its data shows that "long-term use of . . . ephedrine alkaloids, even at relatively low levels, is related to serious adverse events, including cardiomyopathy and myocardial necrosis."[20],[21] However, the presence of ephedrine alkaloids in the body is not dispositive of the fact that cardiomyopathy was the result. Reliance on AERs to prove cardiomyopathy is inappropriate because of he prevalence of the disease in the general population. According to the Montgomery Heart Foundation for Cardiomyophathy,[22] approximately one in 500 people carry an altered gene that can cause certain forms of the disease. Therefore, many who suffer or die from this disease, contracted it genetically. Others contract it through infection, endocrine disorders, metabolic disorders or other

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[17] *Id.*
[18] *Id.* at 30,694.
[19] *Id.* at 30,707 (emphasis added).
[20] *Id.* at 30,695.
[21] Cardiomyopahty is a structural or functional abnormality of the heart muscle, causing weakening of the heart muscle and subsequent inability of the heart to pump blood efficiently.
[22] The Montgomery Heart Foundation for Cardiomyopathy is the only organization in the country whose primary focus is cardiomyopathy, and is the sole advocate for research in the treatment of the disease as well as a clearinghouse for current information on the subject.

unknown causes. The agency has not identified any test or assay to prove dispositively that any reported incidents of cardiomyopathy truly are due to long-term use of ephedrine alkaloids. In fact, literature on the subject suggests that no such test exists.

D. Labeling Language

The proposed rule also contains provisions regarding new label requirements. The statement, "Do not use this product for more than 7 days,"[23] clearly would eliminate the product for use as a weight loss supplement as discussed earlier. However, as discussed above, no scientific evidence supports the statement. FDA's rationale for this statement is that weight loss claims, for instance, promote excessive consumption. However, it is not at all clear how weight loss claims can be differentiated from any other beneficial effect, or why beneficial effects automatically entice consumers to exceed the recommended dosage.

Similarly, the proposed "death" warning is unsubstantiated. The statement, "Taking more than the recommended serving may cause heart attack, stroke, seizure, or death," is at best, an over statement—at least based on the scientific evidence presented by FDA. In addition to the lack of scientific evidence, FDA's actions in the case of the death warning seem arbitrary and capricious because no such warning appears on over-the-counter (OTC) ephedrine products (pharmaceutical derivations). There is the appearance that FDA is arbitrarily singling out one industry for regulation.

If any label statement were to be required, the Office of Advocacy recommends label statements similar to those currently found on OTC ephedrine products.

III. Unfunded Mandates Act

The agency apparently has also overlooked the requirements of the Unfunded Mandates Reform Act (UMRA)[24], which, as of 1995, applies not only to states, but also to private industry (including all sizes of businesses). UMRA, therefore, applies in the case of a federal private sector mandate where the aggregate estimated amounts that the private sector will be required to spend in one year in order to comply with the mandate exceeds $100 million. If the agency had performed an adequate analysis, it would have been apparent that the economic impact of the instant rule would impose in excess of $100 million in costs to the industry.

When UMRA applies, an agency must issue a written statement containing specific information and the agency shall also "identify and consider a reasonable number of regulatory alternatives and from those alternatives select the least costly, most cost-effective or least burdensome alternative that achieves the objectives of the rule."[25] Among other things, an agency's written statement must contain the following:

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[23] 62 Fed. Reg. at 30,718.
[24] Pub. L. No. 104-4, 109 Stat. 48, (1995), (codified as amended in 2 U.S.C. §§ 1501-71 (Supp. 1996)).
[25] 2 U.S.C. at § 1535(a).

- a qualitative and quantitative assessment of the anticipated costs and benefits of the federal mandate, including the costs and benefits to the private sector, as wel as the effect of the federal mandate on health, safety, and the natural environmen
- estimates by the agency, if and to the extent that the agency determines that accurate estimates are reasonably feasible, of the future compliance costs; and an disproportionate budgetary effects of the federal mandate upon any particular regions of the nation or particular segments of the private sector; and
- estimates by the agency of the effect on the national economy, such as the effect on productivity, economic growth, full employment, creation of productive jobs, and international competitiveness of U.S. goods and services.

There was no such written statement in the instant rulemaking because the agency di not even identify Unfunded Mandates as an issue.
The burden of achieving reduced economic impact for businesses subject to a regulation is higher in the case of UMRA than for the RFA. That is, the RFA require only that agencies endeavor to reduce economic burden where possible by carefully analyzing and selecting less burdensome alternatives in the scheme of the agency's regulatory objectives. However, modifiers like "most" and "least" are used in describing the requirements of UMRA—the "least burdensome alternative", for example.

It is the opinion of the Office of Advocacy that the instant rule is not the least costly, most cost-effective or least burdensome alternative for reasons previously expressed. In addition, the agency has not provided any explanation (as required by UMRA) as t why it has not complied with the requirements.

IV. Administrative Procedure Act

The APA requires an agency to publish a notice of proposed rulemaking in the *Federal Register* and to provide the public with an opportunity to comment. 5 U.S.C. § 553. The notice and comment requirements of the APA serve three distinct purposes:

> [f]irst, notice improves the quality of agency rulemaking by ensuring that agency regulations will be "tested by exposure to diverse public comments: Second, notice and the opportunity to be heard are an essential component of "fairness to affected parties." Third, by giving affected parties an opportunity to develop evidence in the record to support their objections to a rule, notice enhances the quality of judicial review."

Small Refiner Lead Phase-Down Task Force v. EPA, 705 F.2d 506, 547 (D.C. Cir. 1983) (citations omitted). Most importantly, the notice must "provide sufficient detail and rationale for the rule to permit interested parties to participate meaningfully." Horsehead Resource Dev. Co. v. Browner, 16 F.3d 1246, 1268 (D.C. Cir. 1994), cert. denied, 115 S. Ct. 72 (1994). Furthermore, an agency:

must describe the range of alternatives being considered with reasonable specificity. Otherwise, interested parties will not know what to comment on, and notice will not lead to better-informed agency decision-making. Id. at 1268.

In this case, FDA failed to establish a record upon which the public and affected entities could comment. There simply is not enough relevant information or data in the instant rulemaking for there to be adequate notice to the public regarding the likely impact of the regulation.

Moreover, the method in which the record was updated and corrected placed a great burden on those entities attempting to decipher the administrative record on file at the agency.[26] Although the comment period was extended while adjustments were made to the record, the new materials apparently were lumped together with the original documents making it impossible to determine which materials were new. It was necessary, therefore, to undergo the expensive and time consuming task of reviewing the entire record to find the new information.

V. Other Alternatives

FDA proposes implementation of the rule 180 days after publication of the final rule.[27] This seems unreasonable. The agency did not consider any alternative length of time for implementation. FDA does reference the fact that businesses were given 18 months to comply with the regulation for nutrition labeling of dietary supplements,[28] but did not explain why 6 months was an adequate period of time in the instant case.

FDA should extend the length of time for compliance. The time required for reformulation of many products and printing new labels may be considerable and should be a major consideration. The Office of Advocacy suggests a period of not less than one year, but we defer the to the judgment and expertise of the industry if they determine that a period longer than one year is needed to comply.

VI. Conclusion

Under no circumstances would the Office of Advocacy support any business, small or otherwise, that produces or sells misbranded or adulterated products to consumers. However, it is not clear why this rule will accomplish more than adequately enforced laws already in existence. Currently, unsafe or adulterated products that harm consumers may be seized or removed from the stores under FDA's present authority. Moreover, false claims in advertising can be addressed on a case-by-case basis by the Federal Trade Commission. These alternatives warrant greater analysis.

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[26] Under § 609(a)(5) of the RFA,

"when any rule is promulgated which will have a significant economic impact on a substantial number of small entities, the head of the agency . . . with statutory responsibility for the promulgation of the rule shall assure that small entities have been given an opportunity to participate in the rulemaking for the rule through the reasonable use of techniques such as— . . . the adoption or modification of agency procedural rules to reduce the cost or complexity of participation in the rulemaking by small entities."

[27] 62 Fed. Reg. at 30,709.

[28] *See* 60 Fed. Reg. 67,184 (December 28, 1995).

The Office of Advocacy realizes that industry data and conclusions regarding this or any other proposed rule many be somewhat skewed or self serving, but the information provided by the industry in this instance is so compelling and so different from the information provided by FDA, that the agency needs to address these serious concerns before publishing a final rule. FDA can accomplish this only through better data and more science-based analysis.

The agency's claims regarding market failure and adverse event reports have no basis in science. Similarly, the dosage restrictions in the instant case have no scientific basis and practically prohibit small entity participation in free market competition. Without more specific scientific evidence and analysis, to require anything more than label warnings about possible reactions or drug interactions would likely be in violation of the Regulatory Flexibility Act, the Administrative Procedure Act, the Unfunded Mandates Act and Executive Order 12,866.

Sincerely,

Jere W. Glover
Chief Counsel for Advocacy

Shawne Carter McGibbon
Asst. Chief Counsel for Advocacy

ATTACHMENT B

HAUSER®

April 8, 1998
Test Report No. C8-0730

CLIENT: Metabolife International Inc.
5070 Santa Fe Street
San Diego, CA 92109

Attn: Mike Ellis

SAMPLES: One case of Metabolife Dietary Supplement 356 was received March 23, 1998. The label listing the ingredients in this product is attached.

TESTS: It was requested that we attempt to produce methamphetamines from the Metabolife Dietary Supplement using the "street" method published in The Journal of Forensic Sciences, Vol. 40, No. 4, July 1995.

RESULTS: The tablets were initially analyzed for ephedra content by High Performance Liquid Chromatography (HPLC). Each tablet was found to contain 13.1 mg/tablet on average of ephedra alkaloids.
The contents of the 12 bottles of Metabolife Dietary Supplement 356 were ground resulting in approximately 1.3 kg of starting material (13.7 g ephedra alkaloids). The material was extracted into methanol and the extract was reacted with red phosphorus and hydriodic acid for five hours. The resulting mixture was basified and extracted into freon. The freon was then acidified using hydrogen chloride gas. This should have resulted in the production of methamphetamine crystals, however it formed a black tar like material. The material was tested by Gas Chromatography/Mass Spectroscopy (GC/MS) and found to contain mostly ephedra alkaloids and caffeine, the presence of methamphetamine was not detected.

CONCLUSION: The procedure described above was performed according to the method published in The Journal of Forensic Sciences, Vol. 40, No 4, July 1995, titled "Ephedra's Role As a Precursor in the Clandestine Manufacture of Methamphetamine" by K.M. Andrews. Based on our analysis, it does not appear that this published method can be used to make methamphetamine from Metabolife's Dietary Supplement 356.

REPORT WRITTEN
& ANALYSIS PERFORMED BY:

J. Scott Moore
Technician III

REPORT REVIEWED BY:

Nicole M. Enderle
Chemist

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